



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA 2016-D-4460]

Multiple Endpoints in Clinical Trials; Guidance for Industry; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of availability.

SUMMARY: The Food and Drug Administration (FDA or Agency) is announcing the availability of a final guidance for industry entitled “Multiple Endpoints in Clinical Trials.” This guidance provides sponsors and review staff with the Agency’s thinking about the problems posed by multiple endpoints in the analysis and interpretation of study results and how these problems can be managed in clinical trials for human drugs, including drugs subject to licensing as biological products. This guidance finalizes the draft guidance of the same title issued on January 13, 2017.

DATES: The announcement of the guidance is published in the *Federal Register* on [INSERT DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

ADDRESSES: You may submit comments on any guidance at any time as follows:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <https://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <https://www.regulations.gov> will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else’s Social Security number, or confidential business information, such as a manufacturing process. Please note that if

you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on <https://www.regulations.gov>.

- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see “Written/Paper Submissions” and “Instructions”).

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in “Instructions.”

Instructions: All submissions received must include the Docket No. FDA 2016-D-4460 for “Multiple Endpoints in Clinical Trials.” Received comments will be placed in the docket and, except for those submitted as “Confidential Submissions,” publicly viewable at <https://www.regulations.gov> or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240-402-7500.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states “THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.” The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out,

will be available for public viewing and posted on <https://www.regulations.gov>. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as “confidential.” Any information marked as “confidential” will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA’s posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: <https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf>.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to <https://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the “Search” box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500.

You may submit comments on any guidance at any time (see 21 CFR 10.115(g)(5)).

Submit written requests for single copies of this guidance to the Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration, 10001 New Hampshire Ave., Hillandale Building, 4th Floor, Silver Spring, MD 20993-0002 or to the Office of Communication, Outreach and Development, Center for Biologics Evaluation and Research (CBER), Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002. Send one self-addressed adhesive label to assist that office in processing your requests. See the SUPPLEMENTARY INFORMATION section for electronic access to the guidance document.

FOR FURTHER INFORMATION CONTACT: Scott N. Goldie, Center for Drug Evaluation and Research, Office of Biostatistics, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 21, Rm. 3557, Silver Spring, MD 20993-0002, 301-796-2055, or Stephen Ripley,

Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 7301, Silver Spring, MD 20993-0002, 240-402-7911.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a guidance for industry entitled “Multiple Endpoints in Clinical Trials.” This guidance describes various strategies for grouping and ordering endpoints for analysis of a drug’s effects and applying some well-recognized statistical methods for managing multiplicity within a clinical trial to control the chance of making erroneous conclusions about a drug’s effects. FDA’s International Conference on Harmonization (ICH) guidance for industry “E9 Statistical Principles for Clinical Trials” is a broad-ranging guidance that includes discussion of multiple endpoints. This guidance provides greater detail on the topic of multiple endpoints.

Failure to account for multiplicity when there are several clinical endpoints evaluated in a clinical trial can lead to false positive conclusions regarding the effects of the drug. The regulatory concern regarding multiplicity arises principally in the evaluation of clinical trials intended to demonstrate effectiveness and support drug approval; however, this issue is important throughout the drug development process.

The focus of this guidance is control of the Type 1 error rate for the planned primary and secondary endpoints of a clinical trial so that the major findings are well supported. Multiplicity adjustments provide a means for controlling the Type 1 error rate when there are multiple analyses of the drug’s effects. The issues of multiplicity and methods to address them are illustrated in the guidance with examples of different study endpoints. Both the issues and methods that apply to multiple endpoints also apply to other sources of multiplicity, including multiple doses, time points, or study population subgroups.

This guidance finalizes the draft guidance of the same title that published January 13, 2017 (82 FR 4353). FDA considered comments received on the draft guidance as the guidance

was finalized. Changes from the draft to the final guidance include clarifications for some of the potential issues caused by including multiple endpoints in clinical trials and clarifications for some of the strategies for handling these issues. In addition, editorial changes were made to improve clarity by reducing redundancies in the text.

This guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The guidance represents the current thinking of FDA on "Multiple Endpoints in Clinical Trials." It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations.

II. Paperwork Reduction Act of 1995

While this guidance contains no collection of information, it does refer to previously approved FDA collections of information. Therefore, clearance by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (PRA) (44 U.S.C. 3501-3521) is not required for this guidance. The previously approved collections of information are subject to review by OMB under the PRA. The collections of information in 21 CFR 312.23 for the content and format of investigational new drug applications have been approved under OMB control number 0910-0014. The collections of information in 21 CFR part 314 for submitting applications for FDA approval to market a new drug have been approved under OMB control number 0910-0001. The collections of information in 21 CFR 201.56 and 201.57 for preparing and submitting labeling have been approved under OMB control number 0910-0572.

III. Electronic Access

Persons with access to the internet may obtain the guidance at <https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs>, <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>, or <https://www.regulations.gov>.

Dated: October 17, 2022.

Lauren K. Roth,

Associate Commissioner for Policy.

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